UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/528,824	03/23/2005	Alain Rambach	37991-0035	6976

26633 7590 07/11/2007

HELLER EHRMAN LLP
1717 RHODE ISLAND AVE, NW
WASHINGTON, DC 20036-3001

EXAMINER	
PETERSEN, CLARK D	

ART UNIT	PAPER NUMBER
1657	

MAIL DATE	DELIVERY MODE
07/11/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/528,824	RAMBACH ET AL.	
	Examiner	Art Unit	
	Clark D. Petersen	1657	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 April 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,3,7,8,10-12,14 and 16* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,7,8,10-12,14 and 16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This action is in response to the amendment, filed 30 April 2007, in which claim 15 was canceled and claims 1, 11, and 14 were amended.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

All objections and rejections not repeated in the instant Action have been withdrawn due to Applicant's response to the previous Action.

Claim Rejections - 35 USC § 112

Claims 1, 3, 7, 8, and 10-12 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites a medium for detecting *S. aureus* "after an enriching phase". This phrase leaves it unclear what the sample is enriched for, and the specification does not provide any guidance, but rather recites the exact language used in the claim. Therefore it would not be clear to one of ordinary skill in the art what property or substance would be enriched. Claims 3, 7, 8, and 10-12 are rejected because they depend from claim 1.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 10, and 11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merlino et al (J Clin Microbiol, June 2000) in view of Felten (J Clin Microbiol, Aug 2002).

This rejection was first presented in the Office Action mailed 29 January 2007 and is maintained for reasons of record and as set forth below.

Merlino et al teach that methicillin-resistant *Staphylococcus aureus* can be detected by plating on the solid medium CHROMagar, which contains a proprietary mix of chromogenic agents that change color when metabolized by *Staphylococcus aureus* (see Introduction, p. 2378, for example). They report that methicillin-resistant bacteria reliably grew on methicillin/oxacillin-doped plates, and that the color change afforded by the CHROMagar medium reliably discerned between *S. aureus* and non-staphylococcal species (see Results, p. 2380, col. 1, for example).

Merlino does not teach the use of the claimed cephalosporin antibiotics as selective agents in a chromogenic medium.

Felten et al teach that it is difficult on occasion to discern class 1 MRSA *S. aureus* from methicillin-susceptible *S. aureus* with standard oxacillin-resistance tests

(see Abstract and Introduction, for example). They report that testing a MRSA type 1 strain with cefoxitin or moxalactam led to 100% identification of MRSA type 1 strains as being methicillin-resistant, which is an improvement over the reliability of oxacillin testing, as taught be Merlino et al (see Felten et al, p. 2768, Table 1 and Results). In particular, Felten et al teach that antibiotic susceptibility tests can be carried out in medium containing no salt or 2% salt (see p. 2767, col. 1, first paragraph for example). There is no mention of adding salt in medium containing moxalactam (see p. 2767, col. 2, sections (ii) to (iv), for example). Moxalactam, for example, was added to MHA medium before solidification at a concentration of 0.5 to 32 mg/L (see p. 2767, col. 2, section (iv).

A person of ordinary skill in the art at the time the invention was made would have been motivated to test MRSA resistance among *S. aureus* strains in a method taught by Merlino et al using antibiotic resistance testing taught by Felten et al, because Merlino et al teach that one can distinguish reliably distinguish *S. aureus* from other strains of *Staphylococcus* using a chromogenic reagent, and Felten et al teach that one can more reliably detect low-level methicillin resistance using later generation cephalosporins like cefoxitin and moxalactam.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to test for methicillin resistant *S. aureus* strains by testing antibiotic resistance with moxalactam or cefoxitin, and ensure proper species recognition with a chromogenic reagent when attempting to characterize clinical bacterial isolates.

Claims 1 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merlino (J Clin Microbiol, June 2000) in view of Felten (J Clin Microbiol, Aug 2002) and in view of Boggs et al (US Patent # 5,883,074, issued 16 March 1999).

This rejection was first presented in the Office Action mailed 29 January 2007 and is maintained for reasons of record and as set forth below.

The teachings of Merlino et al and Felten et al are discussed above and applied as before.

Merlino et al and Felten et al do not expressly teach the use of cefamandole and cefotetan in a method of detecting MRSA bacteria.

Boggs et al teach that MRSA *S. aureus* develop resistance to numerous antibiotics (see Summary of the Invention, col. 1 line 48 to col 2 line 40, for example). Boggs et al teach that one must selectively grow MRSA *S. aureus* by including an antibiotic; this antibiotic can be cefamandole, cefoxitin, or cefotetan (see col. 4 line 56 to col. 5 line 13; see col. 6, lines 13-25, for example).

A person of ordinary skill in the art at the time the invention was made would have been motivated to include cefamandole, cefoxitin, or cefotetan because Boggs et al teach that MRSA *S. aureus* are often selectively resistant to these drugs.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to test for MRSA resistance in *S. aureus* using a S. aureus-selective chromogenic medium and cefamandole, cefoxitin, or cefotetan as selective antibiotics.

Claims 1 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merlino (J Clin Microbiol, June 2000) in view of Felten (J Clin Microbiol, Aug 2002) and in view of Dorso et al (US Patent # 6,221,859, issued 24 April 2001).

This rejection was first presented in the Office Action mailed 29 January 2007 and is maintained for reasons of record and as set forth below.

The teachings of Merlino et al and Felton et al are discussed above and applied as before.

Merlino et al and Felten et al do not expressly teach the use of cefmetazole in a method of detecting MRSA bacteria.

Dorso et al teach a method of treating antibiotic resistant *S. aureus*, among other types of pathogenic bacteria (see Abstract, see Summary of the Invention, col. 1 line 59 to col. 2, line 5, for example). They teach that cefmetazole is among the antibiotics that are losing efficacy against pathogenic bacteria, and must be combined with other compounds to enhance treatment (see col. 8, line 63 to col. 9, line 10, for example).

A person of ordinary skill in the art at the time the invention was made would have been motivated to include cefmetazole in a selective medium for detecting resistant *S. aureus*, because Dorso et al teach that cefmetazole is a compound that is subject to bacterial resistance, and Felten et al and Merlino et al teach a method of detecting *S. aureus* with resistance to a given antibiotic.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to test *S. aureus* resistance against cefmetazole by culturing on a medium containing cefmetazole and a chromogenic reagent.

Claims 1 and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merlino (J Clin Microbiol, June 2000) in view of Felten (J Clin Microbiol, Aug 2002) and in view of Hanaki (US Patent # 6,294,527, issued 25 Sep 2001).

This rejection was first presented in the Office Action mailed 29 January 2007 and is maintained for reasons of record and as set forth below.

The teachings of Merlino et al and Felton et al are discussed above and applied as before.

Merlino et al and Felten et al do not expressly teach the use of flomoxef in a method of detecting MRSA bacteria.

Hanaki et al use flomoxef-doped plates as a control for testing other compounds against *S. aureus* bacteria. Use of flomoxef as a control distinctly shows its use for characterizing MRSA *S. aureus* versus non-resistant *S. aureus*. Flomoxef has no effectiveness against MRSA bacteria, but is extremely effective against non-resistant bacteria (see col. 11 line 52 to col. 12 line 35; see Table 1, col. 12, as examples).

A person of ordinary skill in the art at the time the invention was made would have been motivated to include flomoxef in a selective medium for detecting resistant *S. aureus*, because Hanaki et al teach that flomoxef is a compound that is subject to bacterial resistance, and Felten et al and Merlino et al teach a method of detecting *S. aureus* with resistance to a given antibiotic.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to test whether *S. aureus* has MRSA characteristics by culturing on a medium containing flomoxef and a chromogenic reagent.

Claims 1, 3, 7, 8, and 10-12 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merlino et al (J Clin Microbiol, June 2000) in view of Felten et al (J Clin Microbiol, Aug 2002) and in view of Rambach (US Patent # 6,548,268, issued 15 Apr 2003, claiming priority to 9 Mar 2000).

This rejection was first presented in the Office Action mailed 29 January 2007 and is maintained for reasons of record and as set forth below.

The teachings of Merlino et al and Felten et al are discussed above and applied as before.

Merlino et al and Felten et al do not expressly teach the use of 5-bromo-4-chloro-3-indoxyl glucoside, 5-bromo-6-chloro-3-indoxyl phosphate, or 5-bromo-4-chloro-3-indoxyl glucuronide as chromogenic reagents.

Rambach teaches that these reagents are effective chromogenic reagents for detecting *S. aureus*. Rambach teaches that each of the above chromogenic dyes can be used to detect growth of *S. aureus*, which generates a different color in the presence of the substrate than other *Staphylococcus* species in particular, and other bacterial species generally (see column 2, lines 12-17; see column 2 lines 32-39, as examples). Additionally Rambach expressly endorses adding two or all three chromogenic substrates together for optimal detection of *S. aureus* (see lines 32-39, for example).

Specifically, Rambach teaches that indoxyl phosphate or glucoside should be used as a first chromogen; the selectivity is enhanced if indoxyl glucuronide is added as well, reading on instant claims 3, 7, and 8 (see col. 2, lines 12-39, for example). Additionally Rambach teaches that indoxyl glucoside can be included, reading on claim 16. These chromogens can be included at a concentration of 0.05 g/l (see col. 2, lines 55-60, for example).

A person of ordinary skill in the art at the time the invention was made would have been motivated to use the chromogenic substrates taught by Rambach et al in a method of detecting MRSA *S. aureus* taught by Merlino et al and Felten et al, because Merlino et al teach that chromogenic substrates can be used to detect MRSA *S. aureus*, Felten et al teach that cefoxitin and moxalactam can be used to detect low-resistance *S. aureus*, and because Rambach teaches that *S. aureus* can be specifically identified by growing on the chromogenic substrates identified in his patent publication.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to identify MRSA *S. aureus* as taught by Merlino et al and Felten et al using the chromogenic substrates taught by Rambach.

Claims 1, 10, 11 and 14 are rejected under 35 U.S.C. 103(a) as being unpatentable over Merlino et al (J Clin Microbiol, June 2000) in view of Felten (J Clin Microbiol, Aug 2002), in view of Carricajo et al (Eur J Clin Microbiol Infect Dis, 1999) and in view of Pead et al (J Clin Pathol, 1977).

This is a new rejection necessitated by Applicants' amendment.

The teachings of Merlino et al and Felten et al are discussed above and applied as before.

Neither reference expressly teaches that samples should be directly taken from patients without further manipulation of the samples.

Carricajo et al teach that one can test clinical urine specimens by direct inoculation onto chromogenic media. Specifically, they teach that types of staphylococci can be differentiated by inoculating small samples of urine directly onto CHROMagar with an inoculating loop (see Materials and Methods, p. 797-8, for example).

Pead et al teach that in a survey of staphylococcus as determined from urine samples, *S. aureus* is responsible for 16% of infections (see Abstract, p. 427).

A person of ordinary skill in the art at the time the invention was made would have been motivated to test clinical samples for the presence of *S. aureus* by direct inoculation of clinical samples onto a chromogenic medium because Carricajo et al teach that one can directly inoculate urine onto CHROMagar medium and observe development of staphylococcus specimens, and Pead et al teach that *S. aureus* infections are a substantial fraction of staphylococcus infections as determined by urine samples.

Hence, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to inoculate chromogenic media directly from clinical samples in a method of testing for the presence of *S. aureus*.

Response to arguments – Claims Objections

Based on Applicants' amendment to claims 1 and 14, the claims objections presented in the Office Action mailed 29 January 2007 are withdrawn.

Response to arguments - 35 USC § 112

Based on Applicants' amendment to claim 11, the rejection under 35 USC 112, second paragraph, in the Office Action mailed 29 January 2007 is withdrawn.

Response to arguments – Double Patenting

Examiner acknowledges Applicants' response to the rejection of claims 1, 3, 7, 8, 14; and 16 on the ground of non-statutory double patenting over claims 1-12 of co-pending U.S. Application No. 10/753,417. Based on the fact that Application No. 10/753,417 has been abandoned, this rejection is withdrawn.

Response to arguments - 35 USC § 103

Applicants traverse the rejection of claims 1, 10, 11, and 14 in the Office Action mailed 29 January 2007 under 35 USC 103(a) as being unpatentable over Merlino et al in view of Felten et al. Applicants argue that neither Merlino nor Felten teaches a medium for growing MRSA in a sample from a patient, either directly applied to the medium, or applied after an enriching phase. Applicants assert that Merlino and Felten do not teach a recited antibiotic *within* the culture medium. Applicants argue that Felten only teaches the culture of *isolates* from S. aureus-infected patients.

Applicants' arguments have been fully considered but are not deemed persuasive.

As discussed above, the term "an enriching phase" is unclear. However in one embodiment an enriching phase might consist of expanding a *S. aureus* culture derived from a patient sample. This step is taught by Merlino (see "Bacterial cultures", p. 2378, col. 2, for example). They teach that *S. aureus* isolates were cultured from clinical samples of blood, tissue, bone, eye, wounds, etc. The MRSA-positive or -negative character of these isolates was then tested by culturing on CHROMagar containing oxacillin or methicillin. Although Applicants dispute the characterization of these isolates as clinical samples that have gone through an enriching phase, it seems to Examiner that the bacterial isolates taught by Merlino et al fit the limitations as they best can be understood from instant claim 1. Furthermore, it is clear that Merlino et al have a clinical application in mind. The purpose of their study is to characterize chromogenic media for use in clinical laboratories, as is made clear in the Introduction (p. 2378). They believe that their samples are equivalent to clinical specimens, and imply that their study is focused on clinical use:

> Reliable and rapid methods to identify these organisms are crucial in any clinical laboratory. The tube coagulase test is regarded as the gold standard; however, variations in levels in plasma and incubation times and problems in interpretation can lead to misidentification. An alternative approach is to incorporate chromogenic substrates into a suitable isolation medium. Detection of the activities of specific bacterial enzymes, indicated by color change, negates the need for time consuming and costly biochemical identification (Merlino p. 2378 col. 1).

Applicants also argue that Merlino et al teach the use of methicillin or oxacillin as a selective antibiotic, not the instantly claimed antibiotics. However, according to Felten

"The cefoxitin and moxalactam disk diffusion tests were found 100% sensitive and specific for MRSA under all conditions tested...This implies that the cephamycin disk test (cefoxitin or moxalactam) is an available alternative to the oxacillin disk method for routine antibiotic testing (see Discussion, p. 2769)."

Additionally "The strong correlation between cephamycin diameters and oxacillin resistance is mediated by still unknown mechanisms. This strong correlation between cephamycin MICs and methicillin resistance may be due to the interaction between PBP2a and various PBPs by still unknown mechanisms. Compared to cephalosporins, cephamycins have a high affinity for *S. aureus* PBP4, a protein which is involved in cell wall cross-linking. Previous experiments showed a relationship between PBP2, PBP4, and methicillin resistance (Felten, p. 2770, col. 1)." Thus one of ordinary skill in the art would be motivated to add both cephalosporins and cephamycins to media in a method of selectively growing MRSA.

Instant claim 1 only requires that the medium comprise an antibiotic. By the disk diffusion method, antibiotic is locally applied to medium by using small disks as a carrier. However it is understood that the antibiotic diffuses through the medium in a graded fashion. Therefore by application of the disk diffusion method as taught by Felten, for example, the medium does, in fact, contain antibiotic as required in instant claim 1.

Regarding Applicants' argument that the instantly claimed invention fulfills a long felt need, it is irrelevant what the long-felt needs are, because the instantly claimed invention is apparent from combining the references cited by Examiner.

Regarding the teachings of Boggs et al (US 5,883,074), Applicants argue that "Boggs teaches that cefamandole, cefotixin or cefotetan must be combined with a potentiator in order to induce susceptibility in resistant bacteria, and does not therefore teach or suggest that MRSA are often selectively resistant to the anti-bacterials cefamandole, cefotixin or cefotetan alone". Boggs teaches exactly that: methicillin resistant bacteria can grow in the presence of cefamandole, cefotixin or cefotetan alone (i.e. without a potentiator), and therefore inoculation of a medium containing these antibiotics will allow selective growth of methicillin resistant bacteria.

Applicants argue that Dorso et al (US 6,221,859) does not suggest that MRSA bacteria are selectively resistant to cefmetazole. Actually Dorso et al teach that their compositions comprising cefmetazole and another compound are designed to treat MRSA *S. aureus* (see Abstract, for example), directly implying that the antibiotics are not effective alone. Dorso et al teach that cefmetazole is from the class of antibiotics under the umbrella of cephamycems and cephalosporins, growth in the presence of which Felten et al teach (see discussion above) is diagnostic for methicillin resistance.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Clark D. Petersen whose telephone number is (571)272-5358. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon Weber can be reached on (571)272-0925. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

CDP
6/28/2007

Jon Weber
pervisory Patent Examiner